MINI REVIEW

Membranous nephropathy: Recent advances but many remaining questions

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Membranous nephropathy is one of the most common forms of glomerulonephritis, often quoted as the most significant primary cause of nephrotic syndrome in adults. Recent years have seen highly significant advances in the understanding of the pathogenesis, genetic susceptibility and prognosis of the condition but unfortunately these advances have not been matched by improved evidence about the best forms of treatment. The available randomized clinical trials are heterogeneous but mostly too small and/or with follow-up too short and/or with inappropriate design to answer the key questions to which patients and their physicians need to know the answers. The author previously contributed to the primary literature on the disease but for the last 8 years has been working as a university President and so he has no "axe to grind", no conflicts of interest from pharmaceutical consultancies nor any active research programmes and therefore he aims to present impartial analysis of the (unsatisfactory) current situation in relation to this important condition and its treatment.

Key Words: *Membranous nephropathy; Glomerulonephritis; Diagnosis; Hypertension; Proteinuria*

INTRODUCTION

Membranous Nephropathy (MN) is a histological diagnosis associated with the clinical syndrome of proteinuria (Often sufficiently severe to cause nephrotic syndrome) with or without impairment of excretory renal function and/or hypertension. Traditionally reference has been made to a more common "idiopathic" form of the disease and a less common "secondary" form associated with malignancy, infections, lupus or drug toxicity amongst other underlying causes [1]. The "idiopathic" form has long been suspected of having an autoimmune causation but the single biggest recent advance in the understanding of this condition was the description in 2009 by Larry Beck and colleagues of autoantibodies directed against the Phospholipase A2 Receptor (PLA2R) [2]. Soon after, we showed in a European consortium undertaking a definitive study of the genetics of MN that the PLA2R1 gene locus was a highly significant susceptibility locus [3]. In the years since then, it has become ever clearer that the relationship between anti-PLA2R autoantibodies and disease activity, progression, relapse and remission is tight, implying a pathogenetic role [4]. PLA2R is expressed on the glomerular podocyte in man [4] and given the importance of podocyte injury in the causation and prognosis of proteinuria in other forms of glomerular disease, a hypothesis that autoantibody-mediated podocyte injury is the disease mechanism in MN is easy to state (although difficult to prove: the author is aware of several research groups working on the role of PLA2R and anti-PLA2R in podocyte injury but no definitive proof of cellular injury *in vivo*). Around 70-80% of patients previously described as having "idiopathic" MN are now considered to have PLA2R-related disease. Up to another 10% have other autoantibodies of which the most common is anti-thrombospondin type 1 domain containing 7A (THSD7A). A small proportion has no demonstrable autoantibodies using currently available assays.

LITERATURE REVIEW

Therapy of MN

Immunosuppressive drugs were being used for the treatment of MN long before the demonstration of anti-PLA2R or other autoantibodies, but the circumstantial evidence supporting an autoantibody-mediated pathogenesis certainly provides additional rationale for this therapeutic approach. As more specific forms of immuno-modulatory therapy have become available, nephrologists have naturally wished to experiment with them in glomerular diseases for which previous treatments have been so non-specific and therefore potentially toxic. A drug of great interest in glomerular disease in recent years has been rituximab, a chimaeric monoclonal antibody against CD20, a cell surface marker on B lymphocytes [5]. Another hypothesis which it is easy to state is that if autoantibodies cause the disease, a drug which selectively targets the B cell lineage should be very effective because it will destroy the cells producing the autoantibodies. I would sound four notes of caution here: first, because a drug is highly selective does not mean that it is entirely safe and can therefore be used uncritically. There are reports of serious long-term adverse effects associated with rituximab including progressive multifocal leukoencephalopathy, a progressive and rapidly fatal disease [6]. Second, these drugs are expensive and need to be administered repeatedly, so the total costs of treatment can be very high. Third, the enthusiasm for rituximab has in my opinion moved faster than the evidence for its long-term effectiveness: it is important to remember that MN can, and often does, undergo spontaneous remission, so that Randomised Controlled Clinical Trials (RCTs) with long follow-up are essential before firm conclusions about the value of any therapy can be assured. Fourth, those who justify their enthusiasm for rituximab on the basis of its effects on the circulating level of an autoantibody need to remember that the drug seems to also be effective in some forms of nephrotic syndrome where there are no known autoantibodies, particularly Minimal Change Nephropathy (MCN) and Focal Segmental Glomerulosclerosis (FSGS). Whether this is because of an as yet unrecognised role for B cells in the causation of these diseases or (More likely in my opinion) an effect on podocytes [7] remains uncertain.

There is no doubt that the more traditional forms of immunosuppressive therapy, particularly glucocorticosteroids and alkylating agents such as chlorambucil and cyclophosphamide, but also calcineurin inhibitors such as cyclosporin and tacrolimus have very severe toxicity potential. Unfortunately this is particularly the case in patients with impaired excretory renal function. This is important in MN because the best predictor of a poor prognosis in this condition remains the progressive loss of excretory renal function: once decline starts it tends to continue. Whereas severe nephrotic syndrome due to MN can undergo complete spontaneous remission, decline of renal function very rarely does so. This was the rationale behind a RCT

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which the author led, published some 8 years ago now [8] comparing three treatment approaches in bad prognosis patients identified by a progressive decline in excretory renal function. We showed that the combination of corticosteroids and a reduced dose of alkylating agents was the approach most likely to interrupt progression of the disease, but toxicity was high and the responses were only partial in most cases, i.e. slowing of decline but not prevention of it. So, is this approach worth it? Are the risks too high? Is intervening at this late stage doomed to (Partial) failure to prevent end-stage renal disease? Personally I would like to see rituximab and other selective forms of immunotherapy tested in this high risk group. We need RCTs of rituximab compared with prednisolone/alkylating agents which remain the gold standard, if toxic, treatments [1,9]. Also if treatment is to be used in patients with a better prognosis, ie those with well-preserved excretory renal function, this should be in RCTs with long follow-up, comparing to supportive therapy alone i.e. maximal angiotensin pathway blockade plus statins, because without this comparison we can never know for sure that rituximab is altering the natural history of the disease rather than bringing forward remissions which would have happened anyway. The GEMRITUX trial made this comparison and reported no difference in primary end-point between the two groups at 6 months, although analysis at a later time point suggested benefit from rituximab [10]. This is one of the three small, probably all under-powered, RCTs on rituximab that have so far been reported. Clearly larger trials with longer follow-up are still needed. The MENTOR trial compared rituximab with cyclosporin and reported a significant benefit from rituximab at 24 months but not at 12 months [11]. However cyclosporin has been shown to be unsatisfactory in high risk patients [8,9], so that a trial showing that rituximab is superior to an unsatisfactory treatment doesn't answer the key question. The STARMEN trial compared cyclical prednisolone/cyclophosphamide to a slightly odd combination of rituximab with another calcineurin inhibitor tacrolimus and reported that the cyclical therapy was superior [12,13]. Again, this trial does not answer the key questions for nephrologists or indeed for patients with MN: is the current enthusiasm for rituximab justified? When should treatment be initiated? How should poor prognosis patients, who have the most to gain from treatment, be identified before it is too late?

CONCLUSION

The conclusion is inescapable that currently available RCTs do not provide clear guidance about the optimal treatment for MN. A disease with a variable natural history can only be ethically studied by including a conservative treatment group. Waiting until excretory renal function starts to deteriorate might not be in the patients' best interests. An algorithm incorporating anti-PLA2R titre (if positive) as well as traditional markers of poor prognosis such as quantification and duration of proteinuria, excretory renal function, blood pressure, histological features etc. could provide strong predictive value. Long-term follow up, cost-effectiveness analysis and quality of life or other wellbeing measures should be incorporated. Rituximab and other anti-B cell therapies show great promise but it is an indictment of nephrology that several years after the introduction of this form of therapy to the options for glomerular disease we still do not know how to best use it, when to best use it, how safe it is or how cost-effective it is. A literature mainly populated with uncontrolled studies of variable size and duration, studying different dosing schedules, treatment indications, monitoring mechanisms and follow-up indices should embarrass intellectually-rigorous nephrologists into designing and supporting the definitive trials to answer the right questions. Even if you are already convinced (which I am not) that rituximab is a reasonable first-line therapy, what about the 30-40% of patients that don't respond? Surely we need an evidence base for such a large subset of patients.

Future possibilities include podocyte-protective therapies if it is indeed proven that this is the cellular target of the autoimmune responses. Work on MCN and FSGS is highlighting novel therapeutic targets and these could be applied to other diseases where podocyte injury is of causative and prognostic significance. On the assumption that MN is driven by an autoimmune response, it does still seem logical to target the cells that are driving and producing the autoantibodies. B cell responses, including auto reactive B cells, need T cell help and it might be the case that therapy aimed only at B cells is inadequate in the long-term. Specific targeting of T cells is making progress particularly in the field of transplantation: patients with glomerular disease might ultimately benefit as they have done in the past with agents such as corticosteroids, calcineurin inhibitors and biological agents crossing from one part of nephrological practice to another, namely the challenging task of improving the prognosis in primary glomerular diseases such as MN.

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